ERRs Mediate a Metabolic Switch Required for Somatic Cell Reprogramming to Pluripotency.

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Authors: Yasuyuki S Kida, Teruhisa Kawamura, Zong Wei, Takahiro Sogo, Sandra Jacinto, Asako Shigeno, Hiroko Kushige, Eiji Yoshihara, Christopher Liddle, Joseph R Ecker, Ruth T Yu, Annette R Atkins, Michael Downes, Ronald M Evans

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Public Summary:
Cell metabolism is adaptive to extrinsic demands; however, the intrinsic metabolic demands that drive the induced pluripotent stem cell (iPSC) program remain unclear. Although glycolysis increases throughout the reprogramming process, we show that the estrogen-related nuclear receptors (ERRalpha and ERRgamma) and their partnered co-factors PGC-1alpha and PGC-1beta are transiently induced at an early stage, resulting in a burst of oxidative phosphorylation (OXPHOS) activity. Upregulation of ERRalpha or ERRgamma is required for the OXPHOS burst in both human and mouse cells, respectively, as well as iPSC generation itself. Failure to induce this metabolic switch collapses the reprogramming process. Furthermore, we identify a rare pool of Sca1(-)/CD34(-) sortable cells that is highly enriched in bona fide reprogramming progenitors. Transcriptional profiling confirmed that these progenitors are ERRgamma and PGC-1beta positive and have undergone extensive metabolic reprogramming. These studies characterize a previously unrecognized, ERR-dependent metabolic gate prior to establishment of induced pluripotency.

Scientific Abstract:
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